(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76535 A1

(51) International Patent Classification[7]: A61K 38/17, A61P 11/00, C07K 14/785

(21) International Application Number: PCT/EP00/05032

(22) International Filing Date: 2 June 2000 (02.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99111385.3 11 June 1999 (11.06.1999) EP

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(81) Designated States *(national)*: AE, AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/76535 A1

(54) Title: PHARMACEUTICAL PREPARATION CONTAINING MODIFICATIONS OF SURFACTANT PROTEIN B (SP-B) AND SURFACTANT PROTEIN C (SP-C)

(57) Abstract: The invention describes a novel pharmaceutical preparation for treating IRDS or ALI, comprising at least one modification of surfactant protein B (SP-B) and at least one modification of surfactant protein C (SP-C).

PHARMACEUTICAL PREPARATION CONTAINING MODIFICATIONS OF SURFACTANT PROTEIN B (SP-B) AND SURFACTANT PROTEIN C (SP-C)

Technical field of the invention

The invention relates to a novel pharmaceutical preparation which is suitable for the treatment of disease conditions which are designated as Infant Respiratory Distress Syndrome (IRDS) and ALI (Acute Lung Injury), including ARDS.

Prior art

ARDS (**A**cute or **A**dult **R**espiratory **D**istress **S**yndrome) is a descriptive expression which is applied to a large number of acute, diffusively infiltrative pulmonary lesions of different etiology if they are associated with a severe gas exchange disorder (in particular arterial hypoxemia). The expression ARDS is used because of the numerous clinical and pathological features common with IRDS (**I**nfant **R**espiratory **D**istress **S**yndrome). If, in the case of IRDS, the pulmonary surfactant deficiency caused by premature birth is predominant, then in the case of ARDS a pulmonary surfactant malfunction is caused by a lung disorder based on different etiologies.

For many years, IRDS has been treated successfully by introducing pulmonary surfactant preparations into the lungs of the affected children. From pilot studies, it is known that pulmonary surfactant preparations are additionally clinically effective in the case of ALI (**A**cute **L**ung **I**njury) including ARDS (reviewed, for example, by B. Lachmann, D. Gommers and E.P. Eijking: Exogenous surfactant therapy in adults, Atemw.-Lungenkrkh. 1993, 19:581-91; D. Walmrath et al.: Bronchoscopic surfactant administration in patients with severe adult respiratory distress syndrome and sepsis, Am. J. Respir. Crit. Care Med. 1996, 154:57-62; T.J. Gregory et al.: Bovine surfactant therapy for patients with acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 1997, 155: 1309-15).

In this type of treatment, the pulmonary surfactant is either instilled intratracheally as a bolus (IRDS and ARDS) or instilled into individual sections of lung via a bronchoscope (ARDS). V. Balaraman et al. (Physiologic response and lung distribution of lavage versus bolus Exosurf® in piglets with acute lung injury, Am. J. Respir. Crit. Care Med 1996, 153: 1838-43) describe the administration of pulmonary surfactant in an animal model by rinsing in and subsequent drainage. Gommers et al. [Bronchoalveolar lavage with a diluted surfactant suspension prior to surfactant instillation improves the effectiveness of surfactant therapy in experimental acute respiratory distress syndrome (ARDS), Intensive Care Med. 1998, 24: 494-500] describe the carrying-out of a bronchoalveolar lavage (BAL) with dilute surfactant suspension from natural surfactant. Natural pulmonary surfactant is then instilled.

The pulmonary surfactant preparations used for the treatment are compositions having the function of natural pulmonary surfactant. These can be compositions which contain only phospholipids, but also preparations which, in addition to the phospholipids, also contain surfactant protein, inter alia. Commercially available products which may be mentioned are Curosurf® (Serono Pharma GmbH, Unterschleißheim), a highly purified natural surfactant from homogenized pigs lungs, Survanta® (Abbott GmbH, Wiesbaden) and Alveofact® (Dr. Karl Thomae GmbH, Biberach), both extracts of bovine lungs, and also Exosurf® (Deutsche Wellcome GmbH, Burgwedel), a synthetic phospholipid with auxiliaries. Possible pulmonary surfactant proteins are both the proteins obtained from natural sources, such as, for example, pulmonary lavage or extraction from amniotic fluid, and also the genetically engineered or chemically synthesized proteins, and suitable modifications of the surfactant proteins.

The activity, in an animal model, of a pulmonary surfactant preparation which contains a modification of the surfactant protein C [rSP-C (FF/I)] has been described by Häfner et al. (D. Häfner et al.: Effects of rSP-C surfactant on oxygenation and histology in a rat lung lavage model of acute lung injury. Am. J. Respir. Crit. Care Med. 1998, 158: 270-278). Cochran et al. describe the effects of a pulmonary surfactant preparation containing a modification of surfactant protein B in an animal model (Science 1991, 254, 566-568) and in IRDS patients (Pediatric Research 1996, 39, 715-724). This modification has the amino acid sequence KLLLLKLLLLKLLLLKLLLLK (KL4) and is a reconstruction of the hydrophobic-hydrophilic domain of surfactant protein B.

F.J. Walther et al. (Protein Composition of Synthetic Surfactant Affects Gas Exchange in Surfactant Deficient Rats, Pediatric Research 1998, 43, 666-673) describe the effect of different surfactant protein compositions in pulmonary surfactant preparations on the gas exchange in an animal model.

Description of the invention

It is an object of the invention to provide further pulmonary surfactant preparations suitable for the treatment of IRDS and ARDS. Surprisingly, it has now been found that, by adding modifications of surfactant protein C (SP-C) to pulmonary surfactant preparations containing modifications of surfactant protein B (SP-B), pharmaceutical preparations having advantageous properties are obtained.

The invention accordingly provides pharmaceutical preparations comprising at least one modification of SP-B and at least one modification of SP-C.

In the context of the invention, the term "SP-B", in analogy to the nomenclature proposed by Possmayer (Possmayer, F.: A Proposed Nomenclature for Pulmonary Surfactant-associated Proteins. Am.

Rev. Respir. Dis. 1988, 138, 990-998), is to be understood as meaning the surfactant proteins present in natural lung surfactant or amniotic fluid of mammals referred to as SP-B.

The term "modification of SP-B" includes those peptides in which, compared to SP-B, one or more amino acids are missing or have been replaced by other amino acids, as long as the peptides, in a mixture with phospholipids, show pulmonary surfactant activity. The pulmonary surfactant activity can be determined in a manner known to the person skilled in the art. Natural pulmonary surfactant has surface-active properties; for example, it reduces the surface tension in the pulmonary alveoli. A simple and fast in vitro test for the determination of the surface activity of pulmonary surfactant preparations is, for example, the so-called Wilhelmy balance [Goerke, J. Biochim. Biophys. Acta, 344: 241-261 (1974), King R.J. and Clements J.A., Am. J. Physicol. 223: 715-726 (1972)]. This method gives indications about the quality of the pulmonary surfactant, measured as the action of a pulmonary surfactant to achieve a surface tension of almost zero mN/m. Another measuring device for the determination of the surface activity of pulmonary surfactant is the "pulsating bubble surfactometer" [Possmayer F., Yu S. und Weber M., Prog. Resp. Res., Ed. v. Wilchert, Vol. 18: 112-120 (1984)]. The activity of a pulmonary surfactant composition can also be determined by in vivo tests. By the measurement of, for example, the pulmonary compliance, the blood gas exchange or the respiratory pressures needed in animal models of ARDS and IRDS, it is possible to obtain an indication of the activity of a pulmonary surfactant. Such a model is described, for example by Häfner et al. (D. Häfner et al.: Effects of rSP-C surfactant on oxygenation and histology in a rat lung lavage model of acute lung injury. Am. J. Respir. Crit. Care Med. 1998, 158: 270-278). "Modifications of SP-B" is, in particular, also meant to be understood as including those proteins which have an amino acid sequence designed completely independently with a view to its pulmonary surfactant properties, as described, for example, in EP-A-0 593 094, WO 92/22315 and WO 98/49191. In this context, polypeptides selected from the group of polypeptides having the amino acid sequence SEQ ID NO:1 KLLLLKLLLLKLLLLKLLLLK (KL4; INN: sinapultide), SEQ ID NO:2 KLLLLLLLLKLLLLLLLLKLL (KL8), SEQ ID NO:3 KKLLLLLLLKKLLLLLLLKKL (KL7), SEQ ID NO:4 DLLLLDLLLLDLLLLDLLLLD (DL4), SEQ ID NO:5 RLLLLRLLLLRLLLLRLLLLR (RL4), SEQ ID NO:6 RLLLLLLLLRLLLLLLLLRLL (RL8), SEQ ID NO:7 RRLLLLLLLRRLLLLLLLRRL (RL7), SEQ ID NO:8 RLLLLCLLLRLLLLCLLLR (RCL1), SEQ ID NO:9 RLLLLCLLLRLLLLCLLLRLL (RCL2), SEQ ID NO:10 RLLLLCLLRLLLLCLLLRLLLLCLLLR (RCL3) and SEQ ID NO:11 HLLLLHLLLLHLLLLHLLLLH (HL4) may be mentioned by way of example, with KL4 being preferred. These compounds and their preparation are mentioned, for example, in WO 98/49191, with the abbreviations given in brackets being used for characterization.

The abbreviations for the amino acid radicals in the amino acid sequences conform with the Standard Polypeptide Nomenclature (J. Biol. Chem., 243: 3557-59, 1969). The amino acid sequences are shown in the customary short notation, with the amino acid which carries the free amino group at the left end

(amino terminus) and the amino acid which carries the free carboxyl group at the right end (carboxy terminus).

In the context of the invention, the term "surfactant protein C (SP-C)", in analogy to the nomenclature proposed by Possmayer (Possmayer, F.: A Proposed Nomenclature for Pulmonary Surfactant-associated Proteins. Am. Rev. Respir. Dis. 1988, 138, 990-998), is to be understood as meaning the surfactant proteins present in natural lung surfactant or amniotic fluid of mammals referred to as SP-C.

The term "modification of SP-C" includes those peptides in which, compared to SP-C, one or more amino acids are missing or have been replaced by other amino acids, so long as the peptides, in a mixture with phospholipids, show pulmonary surfactant activity. The pulmonary surfactant activity can be determined as described above. Modified derivatives of the pulmonary surfactant proteins designated SP-C which differ from human SP-C in that some amino acids have been replaced are described, for example, in WO 91/18015 and WO 95/32992. In this context, particular emphasis has to be given to the recombinant SP-C derivatives disclosed in WO 95/32992, in particular to the modification which differs from human SP-C in positions 4 and 5 in that cystein has been replaced by phenylalanine and in position 32 in that methionine has been replaced by isoleucin [referred to in WO 95/32992 and hereinbelow as rSP-C (FF/I)].

In addition to the modification of SP-C and the modification of SP-B, the preparations according to the invention comprise, as further components, phospholipids. These are preferably phospholipids which are contained in natural pulmonary surfactant preparations, such as dipalmitoylphosphatidylcholine (DPPC), palmitoyloleylphosphatidylglycerol (POPG) and/or phosphatidylglycerol (PG). Further possible components of the preparations according to the invention are fatty acids, such as, for example, palmitic acid. To adjust a favorable viscosity, the preparations may comprise electrolytes, such as calcium, magnesium and/or sodium salts (for example calcium chloride, sodium chloride or sodium bicarbonate). When determining the type and the amounts of the individual components of the preparations, the person skilled in the art uses, on the one hand, the known composition of natural pulmonary surfactant compositions and, on the other hand, the numerous proposals made in the prior art, such as, for example EP-A 0 119 056 and EP-A 0 406 732.

Preparations according to the invention expediently comprise 80 to 95% by weight of phospholipids, 0.2 to 5% by weight of surfactant proteins (total of the modification of SP-B and the modification of SP-C), 2 to 15% by weight of fatty acids and 0 to 5% by weight of electrolytes (based on the dry weight).

The phospholipids are preferably mixtures of dipalmitoylphosphatidylcholine (DPPC) and palmitoyloleylphosphatidylglycerol (POPG), in particular in a ratio (ratio by weight) of from 7 to 3 to 3 to 7.

Preferred preparations according to the invention comprise 80 to 95% by weight of phospholipids, 0.5 to 3.0% by weight of surfactant proteins (total of the modification of SP-B and the modification of SP-C), 3 to 15% by weight of fatty acid, preferably palmitic acid, and 0 to 3% by weight of calcium chloride (based on the dry weight). The ratio by weight of the modification of SP-B to the modification of SP-C in the preparations according to the invention is preferably 0.3 to 2.0.

Particularly preferred preparations according to the invention comprise 0.2 to 3% by weight of KL4 and 0.2 to 3% by weight of rSP-C (FF/I).

The preparations according to the invention are produced in a manner known to the person skilled in the art, for example by incorporating the surfactant proteins into a phospholipid matrix as described in WO 95/32992. According to the invention, the pulmonary surfactant preparations are preferably provided in lyophilized and in particular in spray-dried form. Lyophilized preparations are known, for example, from WO 97/35882, WO 95/32992, WO 91/00871 and DE 3229179. WO 97/26863 describes a process for preparing pulverulent pulmonary surfactant preparations by spray-drying. According to the invention, preference is given to preparations prepared in this manner.

Below, the production of pharmaceutical preparations according to the invention is described using examples.

Examples

Preparation of pulverulent pulmonary surfactant preparations

Example 1

With heating to 60°C, 3.5 g of 1,2-dipalmitoyl-3-sn-phosphatidylcholine, 1.25 g of 1-palmitoyl-2-oleoyl-3-sn-phosphatidylglycerol sodium, 102.5 mg of calcium chloride dihydrate and 125 mg of palmitic acid are dissolved in 150 ml of ethanol/water (85:15), and the mixture is cooled to room temperature and mixed with 175 ml of a solution of rSP-C (FF/I) in chloroform/methanol 9:1 (c = 429 mg/l) and with 150 ml of a solution of KL4 in chloroform/methanol 9:1 (c = 500 mg/l). The resulting solution is spray-dried in a Büchi B 191 laboratory spray drier. Spraying conditions: gas for drying: nitrogen, inlet temperature 90°C, outlet temperature 52-54°C. This gives a fluffy powder.

Example 2

900 mg of 1,2-dipalmitoyl-3-sn-phosphatidylcholine, 300 mg of 1-palmitoyl-2-oleoyl-3-sn-phosphatidylglycerol ammonium, 180 mg of palmitic acid and 36 mg of KL4 are dissolved in 100 ml of chloroform/methanol 7:3, the mixture is mixed with 60 ml of a solution of rSP-C (FF/I) in 2-propanol/water 95:5 (c = 600 mg/l) and the solution is concentrated using a rotary evaporator. The residue is admixed with 40 ml of water and stirred at 47°C for 15 minutes, and the resulting suspension is divided into 10 ml vials (1 ml per vial) and then lyophilized. Freezing temperature: -40°C, freeze-drying temperature: -20°C, pressure: 0.2 mbar.

Commercial Utility

Adult Respiratory Distress Syndrome (ARDS) is a descriptive expression which is applied to a large number of acute, diffusively infiltrative pulmonary lesions of different etiology if they are associated with a severe gas exchange disorder (in particular arterial hypoxemia). The expression ARDS is used because of the numerous clinical and pathological features common with the Infant Respiratory Distress Syndrome (IRDS). If, in the case of IRDS, the pulmonary surfactant deficiency caused by premature birth is predominant, then in the case of ARDS a pulmonary surfactant malfunction is caused by a lung disorder based on different etiologies. Triggering causes for ALI including ARDS can, for example, be (cited in accordance with Harrison's Principles of Internal Medicine 10th Ed. 1983, McGraw-Hill Int. Book Comp.) diffuse pulmonary infections (for example due to viruses, bacteria, fungi), aspiration of, for example, gastric juice or in the case of near-drowning, inhalation of toxins or irritants (for example chlorine gas, nitrogen oxides, smoke), direct or indirect trauma (for example multiple fractures or pulmonary contusion), systemic reactions to inflammations outside the lung (for example hemorrhagic pancreatitis, gram-negative septicemia), transfusion of high blood volumes or alternatively after cardiopulmonary by-pass.

The preparations according to the invention are not only suitable for the treatment or prophylaxis of IRDS in prematurely born babies or in the treatment or prophylaxis of ALI including ARDS in adults, but also for the treatment or prophylaxis of pneumonia, bronchitis, meconium aspiration syndrome, COPD (chronic obstructive pulmonary disease), asthma and cystic fibrosis.

The administration of the preparations according to the invention is carried out in a manner known to the person skilled in the art, preferably by intratracheal installation (infusion or bolus) or in the form an atomization. For administration, the preparations according to the invention are preferably dissolved or suspended in a suitable solvent or resuspension medium, in particular when the preparations are present in lyophilized or spray-dried form. The suitable solvent is preferably physiological saline. It has been found to be advantageous to administer suspensions or solutions of the preparations according to the invention containing from 12.5 to 100 mg of phospholipids per ml of suspension. Per application, the preparations according to the invention are preferably administered in such an amount that the amount of phospholipids is between 12.5 and 200 mg per kilogram of body weight. Administration is generally carried out once to three times a day over a period of from 1 to 7 days. If desired, a bronchoalveolar lavage, preferably with dilute pulmonary surfactant preparation, can be carried out prior to the administration of the preparations according to the invention. Such a procedure is described, for example, in Gommers et al. [Bronchoalveolar lavage with a diluted surfactant suspension prior to surfactant instillation improves the effectiveness of surfactant therapy in experimental acute respiratory distress syndrome (ARDS), Intensive Care Med. 1998, 24: 494-500] and in WO 98/49191.

Accordingly, the invention also provides a method for the treatment or prophylaxis of pneumonia, bronchitis, meconium aspiration syndrome, COPD, asthma, cystic fibrosis, IRDS and/or ALI (including ARDS) in mammals, in particular humans, by administration of a suitable amount of a pulmonary surfactant preparation according to the invention.

The invention furthermore provides the use of at least one modification of surfactant protein B (SP-B) and at least one modification of surfactant protein C (SP-C) for preparing pharmaceutical preparations (medicaments) for the treatment or prophylaxis of pneumonia, bronchitis, meconium aspiration syndrome, COPD, asthma, cystic fibrosis, IRDS and/or ALI (including ARDS) in mammals, in particular humans.

The invention furthermore provides a commercial product, consisting of a customary secondary pack, a primary pack containing the pharmaceutical preparation (for example an ampoule) and, if desired, an accompanying leaflet, the pharmaceutical preparation being suitable for the treatment or prophylaxis of pneumonia, bronchitis, meconium aspiration syndrome, COPD, asthma, cystic fibrosis, IRDS and/or ALI (including ARDS), the suitability of the pharmaceutical preparation for the prophylaxis or treatment of the disorders mentioned being indicated on the secondary pack or on the accompanying leaflet of the commercial product, and the pharmaceutical preparation comprising at least one modification of surfactant protein B (SP-B) and at least one modification of surfactant protein C (SP-C), together with suitable pharmaceutical auxiliaries. The secondary pack, the primary pack containing the pharmaceutical preparation and the accompanying leaflet otherwise correspond to what the person skilled in the art would consider to be standard for pharmaceutical preparations of this type.

Claims

1. A pharmaceutical preparation for the treatment or prophylaxis of IRDS or ALI, comprising at least one modification of surfactant protein B (SP-B) and at least one modification of surfactant protein C (SP-C).

2. The pharmaceutical preparation as claimed in claim 1, wherein the modification of SP-C is recombinant surfactant protein C FF/I (rSP-C FF/I).

3. The pharmaceutical preparation as claimed in claim 2, wherein the modification of SP-B is selected from the group consisting of SEQ ID NO:1 KLLLLKLLLLKLLLLKLLLLK (KL4), SEQ ID NO:2 KLLLLLLLLKLLLLLLLLKLL (KL8), SEQ ID NO:3 KKLLLLLLLLKKLLLLLLLLKKL (KL7), SEQ ID NO:4 DLLLLDLLLLDLLLLDLLLLD (DL4), SEQ ID NO:5 RLLLLRLLLLRLLLLRLLLLR (RL4), SEQ ID NO:6 RLLLLLLLLRLLLLLLLLRLL (RL8), SEQ ID NO:7 RRLLLLLLLRRLLLLLLLRRL (RL7), SEQ ID NO:8 RLLLLCLLLRLLLLCLLLR (RCL1), SEQ ID NO:9 RLLLLCLLLRLLLLCLLLRLL (RCL2), SEQ ID NO:10 RLLLLCLLRLLLLCLLLRLLLLCLLLR (RCL3) and SEQ ID NO:11 HLLLLHLLLLHLLLLHLLLLH (HL4).

4. The pharmaceutical preparation as claimed in claim 1, wherein the ratio by weight of SP-B to SP-C is from 0.3 to 2.

5. The pharmaceutical preparation as claimed in claim 1, which comprises phospholipids.

6. The pharmaceutical preparation as claimed in claim 5, which comprises, as phospholipids, dipalmitoylphosphatidylcholine (DPPC), palmitoyloleylphosphatidylglycerol (POPG) and/or phosphatidylglycerol (PG).

7. The pharmaceutical preparation as claimed in claim 1, which comprises palmitic acid and electrolytes.

8. The pharmaceutical preparation as claimed in claim 7, which comprises, as electrolytes, calcium salts and/or sodium salts.

SEQUENCE LISTING

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INTERNATIONAL SEARCH REPORT

Inte .ional Application No
PCT/EP 00/05032

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/17 A61P11/00 C07K14/785

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
STRAND, EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 874 406 A (SCHAFER KLAUS PETER ET AL) 23 February 1999 (1999-02-23) cited in the application column 2, line 30 - line 67 column 4, line 39 - line 67 column 7, line 25 -column 8, line 11 claims 1-12 --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2000	03/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stein, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 00/05032

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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